An 82-year-old man with recurrent angioedema

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ABSTRACT

Angioedema is a potentially life-threatening swelling condition that can occur either in isolation or in the context of other syndromes, e.g., *anaphylaxis. Angioedema is typically asymmetric, lasts for hours to days, is not gravity dependent, and is often nonpitting. Recurrent angioedema is typically associated with histaminergic and bradykinin-mediated causes, some of which can indicate underlying etiologies with high morbidity or mortality. The differential diagnosis for acute angioedema can include anaphylaxis, chronic urticaria with angioedema, medications such as angiotensin-converting-enzyme inhibitors, hereditary C1 esterase inhibitor defects, and acquired defects; however, the cause is often idiopathic, and effective therapy can be elusive. In this article, we described a unique etiology of a case of isolated recurrent angioedema that improved when the possible underlying cause was successfully treated.*

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CHIEF CONCERN

Swelling

HISTORY OF PRESENT ILLNESS

The patient was an 82-year-old man with a history of treated prostate cancer, hypertension, and hyperlipidemia who was admitted to our critical care medical unit with oropharyngeal swelling and difficulty handling secretions. There was no concurrent pruritus, urticaria, cough, nausea, vomiting, diarrhea, abdominal pain, chest pain, lightheadedness, or loss of consciousness. He had no fevers, chills, night sweats, or weight loss. He would take occasional nonsteroidal anti-inflammatory drugs for gout, although not recently. Home medications included amlodipine, aspirin, metoprolol, and simvastatin. He experienced one episode of facial angioedema with angiotensin-converting enzyme inhibitor use 20 years earlier, which resolved with medication cessation. Four weeks before presentation, the patient had isolated lip angioedema attributed to chlorthalidone; the medication was stopped and the swelling resolved. He had no other history of swelling, abdominal pain, or urticaria.

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PHYSICAL EXAMINATION

The patient's vital signs included a temperature of 36.4 °C, blood pressure 110/61 mm hg, heart rate 51 beats/minute, and respiratory rate 12 breaths/minute. There was nonpitting angioedema of the lips, face, and tongue (Fig. 1). The lungs were clear to auscultation, without wheezing; heart rate was bradycardic but regular; and the abdomen was without masses or hepatosplenomegaly. There was no urticaria on skin examination. The rest of the examination was unremarkable.

INITIAL LABORATORY AND DIAGNOSTIC FINDINGS

Laboratory analysis demonstrated a hemoglobin of 16.5 g/dL (normal range, 13.5–17 g/dL), platelets were 222,000/mm^3 (normal range, 150,000–400,000/mm^3), and white blood cell count was 7700/mm^3 (4000–10,000/mm^3). The differential included neutrophils, 4100/mm^3; lymphocytes, 2600/mm^3; monocytes, 500 cells/mm^3; and eosinophils, 400 cells/mm^3 (all normal). Results of the patient's chemistries showed a creatinine level of 0.93 mg/dL (normal range, 0.7–1.3 mg/dL), blood urea nitrogen level of 13 mg/dL (normal range, 8–20 mg/dL), and albumin level of 3.4 g/dL (normal range, 3.43–4.84 g/dL).

The patient received epinephrine, antihistamines, and intravenous glucocorticoids without effect. A fiberoptic laryngoscopy showed sparing of the larynx, with unremarkable glottic and supraglottic structures. Due to significant oropharyngeal swelling, the patient underwent intubation. A further laboratory workup was performed. Complement component 4 (C4) was 25 mg/dL (normal range, 13–60 mg/dL), complement

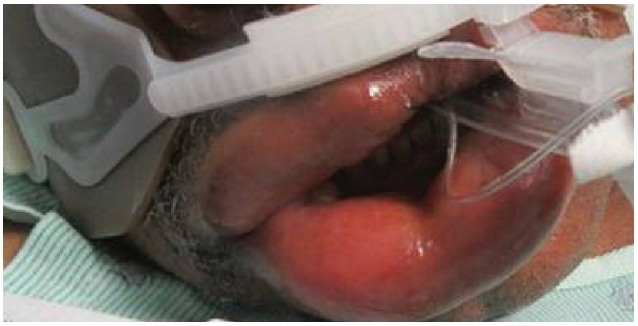

Figure 1. An example of the patient's lip swelling.

component 1q (C1q) was 20 mg/dL (normal range, 12–22 mg/dL), C1 esterase inhibitor function was >90% of normal, and C1 esterase inhibitor antigen was 36 mg/dL (normal range, 13–37 mg/dL). His immunoglobulin G (IgG) level was 1080 mg/dL (normal range, 620-1520 mg/dL), IgA level of 274 mg/dL (normal range, 40–350 mg/dL), and IgM level of 109 mg/dL (normal range, 50–370 mg/dL). The tryptase level was 3.9 ng/mL (normal value, < 11.4 ng/mL). A serum protein electrophoresis with immunofixation showed no M-protein. The prostate specific antigen was 4.2 ng/mL (normal range, 0–6.5 ng/mL), consistent with the patient's known biochemical recurrence and stable over the years. The patient's swelling improved over 2 days, and he was successfully extubated. It was requested that unnecessary medications be stopped; simvastatin and aspirin were discontinued. He was discharged on cetirizine 10 mg daily.

QUESTIONS

What Is the Differential Diagnosis of the Patient's Angioedema?

Angioedema denotes self-limited swelling that occurs from extravasation of fluids.[1,2] Angioedema occurs during anaphylaxis, with acute and/or chronic urticaria, or in isolation. Angioedema is typically asymmetric, with onset of minutes to hours and resolution of hours to days; is not gravity dependent (usually affecting the face, larynx, upper extremities, bowels, and genitals); and is nonpitting.[2]

The differential diagnosis includes histamine- and bradykinin-related angioedema.[2,3] Anaphylaxis may occur due to foods, medications, insect stings, mastocytosis, or other causes; anaphylaxis is typically associated with additional symptoms and has a rapid onset and resolution.[2,3] Chronic urticaria is often idiopathic or related to autoimmune thyroid and rheumatologic diseases.[3] Bradykinin-related angioedema typically does not include other symptoms; causes include hereditary angioedema (HAE), acquired angioedema (often associated with neoplasms, including lymphoma), and medication-related (such as angiotensin-converting enzyme inhibitors or nonsteroidal anti-inflammatory drugs).[3] Many cases of isolated angioedema are idiopathic, although these often respond to oral antihistamines and thus may be histamine related.[2,3] Unusual presentations of hypereosinophilic syndrome or urticarial vasculitis may be considered.[4] Gleich syndrome is a rare disorder that involves episodic angioedema and eosinophilia with an elevated IgM level, followed by increased urine production.[5] Venous thrombosis, such as superior vena cava syndrome, can be mistaken for angioedema, although clotting typically produces durable swelling that does not meet the definition of angioedema.[6]

What Additional Laboratory Data or Investigations Should Be Performed?

A thorough history should evaluate for allergic symptoms, urticaria, pruritus, previous episodes of swelling, drug exposures, insect stings, foods, autoimmune problems, thyroid derangements, and blood clots. Laboratory evaluation should include a sedimentation rate, C-reactive protein, antinuclear antibodies, and thyroid stimulating hormone (TSH) with free T3 and T4. Screening for infectious etiologies, including hepatitis A, B, and C, can be considered. Imaging of the cervical and cerebral vasculature could be pursued to rule out venous thrombosis. With future angioedema episodes, a diagnostic trial of the bradykinin receptor antagonist icatibant would be reasonable to avert intubation; case reports have shown the effects in idiopathic angioedema when given promptly.[7,8]

CLINICAL COURSE

The patient experienced four more episodes of angioedema over the subsequent months; the first required intubation for airway control, and he was extubated after 3 days. A trial of icatibant was unhelpful. The three later episodes were monitored without intubation. Episodes had an onset of several hours and took approximately 3 days to resolve. Angioedema occurred in the absence of other symptoms, such as urticaria, itching, abdominal symptoms, chest pain, dyspnea, or cough. He did not respond to discontinuing amlodipine, increasing cetirizine up to 20 mg twice daily, or adding oral glucocorticoids.

A further imaging and laboratory investigation was undertaken. Diagnostic vascular ultrasound and computed tomography venogram of the head and neck showed no evidence of venous thrombosis. Total hemolytic complement was 74 units/mL (normal range, 41–95 units/mL). Repeated studies, including complete blood cell count, comprehensive metabolic panel, complement component 4 (C4), complement component 1q (C1q), C1 esterase inhibitor antigen and function, remained unchanged. An erythrocyte sedimenta-

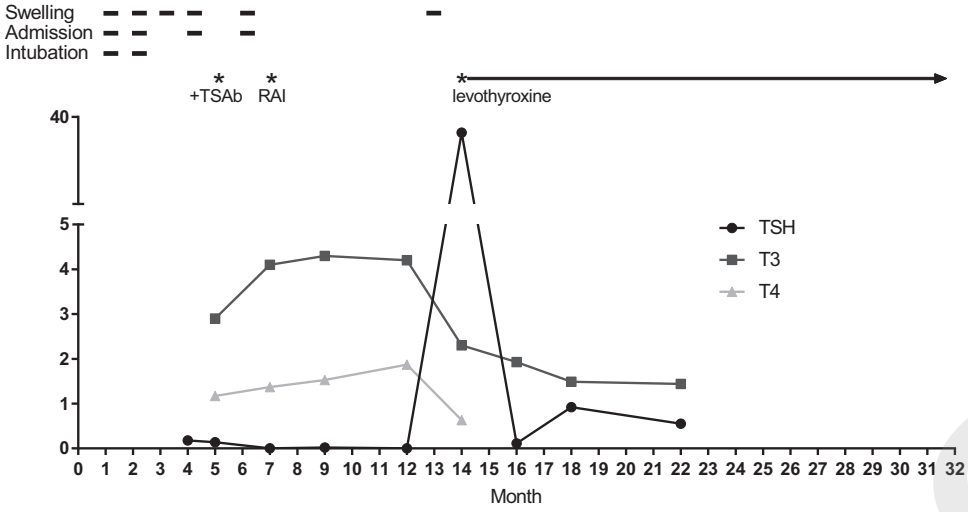

Figure 2. A timeline of the patient's episodes, interventions, and laboratory test results. Thyroid stimulating hormone (TSH) units are mIU/L, free T3 units are pg/mL, and free T4 units are ng/mL. RAI = radioactive iodine ablation; TSAb = thyroid stimulating antibodies.

tion rate was 24 mm (normal range, 0–15 mm). C-reactive protein was 0.6 mg/dL (normal range, 0.0–0.6 mg/dL). Results of an antinuclear antibody screening were negative. Results of hepatitis A IgM, hepatitis B surface antigen, and core IgM, and hepatitis C antibodies were all negative.

A TSH level was 0.18 mIU/L (normal range, 0.3–5.5 mIU/L) and was 0.14 mIU/L on repeated assessment. The free T3 level was 2.9 pg/mL (normal range, 1.9–3.9 pg/mL), and the free T4 level was 1.17 ng/dL (0.76–1.70 ng/dL). Subsequent TSH levels were undetectable; the patient's free T3 level rose to a peak of 4.3 pg/mL, and his free T4 level rose to a peak of 1.87 ng/dL. A thyroid stimulating immunoglobulin index was twice elevated, at 1.9 and 2.0 (normal value, <1.3).

Results of a thyroid iodine uptake scan revealed diffuse uptake throughout the thyroid. The patient was diagnosed with Graves' disease and underwent radioiodine thyroid ablation. He had one additional swelling episode after the ablation before achieving biochemical remission of his Graves' disease. After biochemical remission, the patient was started on levothyroxine replacement. In the subsequent 18 months, he did not experience further angioedema episodes. He restarted his discontinued medications without swelling. He is doing well and living independently. A detailed visual timeline is included in Fig. 2.

DISCUSSION

Isolated, recurrent angioedema is often categorized as histamine or bradykinin related, but frequently is idiopathic.[2,3] Patients who do not fit into a category or respond to therapy may have major consequences, such as airway compromise and intubation.[9] Therefore, an astute clinician must consider uncommon etiologies. Autoimmune thyroid disease has been associated with chronic urticaria and angioedema. Increased levels of antithyroid antibodies are reported in 6.5–57% of patients with chronic urticaria, and the rate may be rising.[10] Whether this represents a causative effect whereby antithyroid antibodies cause urticaria and angioedema, or correlative, whereby such antibodies serve as a marker for another process, is not known.[11]

Graves' disease occurs when auto-antibodies against the TSH receptor lead to inappropriate activation of the thyroid gland and clinical hyperthyroidism.[12] Graves' disease has long been associated with chronic urticaria and angioedema.[13] The rate of Graves' disease in patients with chronic urticaria and angioedema is 0.5–2%.[11] Graves' disease, to our knowledge, has not been associated with isolated angioedema in the absence of urticaria in this manner. One patient has been described with coincidental Graves' disease and HAE but seemed to have two separate processes, which required treatment for both HAE and Graves' disease separately.[14] In our patient's case, HAE was not the likely cause of angioedema, a key difference.

Our patient's case was notable in that his angioedema correlated with the onset and treatment of Graves' disease. This was supported by his initially detectable TSH level, which decreased while the free T3 and T4 levels rose, which co-occurred with his angioedema episodes. The TSH receptors, the main auto-antigen in Graves' disease, are primarily located on thyroid gland cells but are also distributed throughout the body.[12,15] TSH receptor antibodies may spike after radioiodine ablation, which could be related to the patient's episode of angioedema after ablation.[16,17] After radioiodine ablation in Graves' disease, the thyroid stimulating antibodies disappear in the majority of patients.[16] We suspect that, in this case, these antibodies had an off-target effect on nonthyroid tissues, which stimulated his episodes of angioedema and which ceased after biochemical remission, although this point was not provable with the current data. A correlation between Graves' disease and angioedema is

not commonly reported in the literature. This case did not establish causation between these processes but did describe a possible correlation.

CONCLUSION

We reported, to our knowledge, the first case of isolated angioedema directly related to Graves' disease, which ceased after biochemical remission of the Graves' disease. When the clinician encounters isolated angioedema not explained by typical etiologies or responsive to therapy, thyroid screening may be warranted. This case suggests that Graves' disease may coincide with isolated angioedema and that the treatment of the thyroid process may be correlated with cessation of angioedema episodes.

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